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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/417,226	10/13/99	SUNDREHAGEN E	REF/SUNDREHA

HM22/0127

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EXAMINER	
HINES, J	
ART UNIT	**PAPER NUMBER**
1641	2

DATE MAILED: 01/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/417,226	Applicant(s) Sundrehagen et al.
	Examiner Ja-Na Hines	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Oct 13, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-49* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-49* is/are rejected.

☒ Claim(s) *26 and 39* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Arrangement of the Specification

1. The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.

(b) Cross-References to Related Applications.

© Statement Regarding Federally Sponsored Research or Development.

(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).

(e) Background of the Invention.

1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.

(g) Brief Description of the Several Views of the Drawing(s).

(h) Detailed Description of the Invention.

(I) Claim or Claims (commencing on a separate sheet).

(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.

(l) Sequence Listing (see 37 CFR 1.821-1.825).

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

4. Claim 26 is objected to because of the following informalities: The claim refers to "further c..." and is therefore incomplete. Appropriate correction is required.

5. Claim 39 is objected to because of the following informalities: The claim uses "holo=TC II" instead of holo-TC II. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite because of the use of the acronym TC. The acronym must be spelled out when used for the first time in a chain of claims.

7. Claim 4 uses the term "amenable to" and therefore renders the claim indefinite. It is unclear what type of analysis by automated processes are amenable and what types of processes are not amenable to analysis.

8. Claims 5 and 6 are indefinite. Claim 5 is vague because it recites improper Markush language- "selected from the group comprising"; should be --selected from the group consisting of polyclonal or monoclonal antibody.....**and** should replace or before the last member of the Markush group to close the Markush group.

9. Claims 42 and 43 are indefinite. See rejection as stated in claim 5.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 5-7, 12, 41-43, 45-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Quados et al. Quados et al., teaches the characterization of monoclonal antibodies to epitopes of human transcobalamin II (TCII). TC-II was purified from human plasma (page 150 para .1). Based on the interaction with three different regions of the protein, three types of functional monoclonal antibodies were generated (abstract). The first type of antibody binds holo-TCII and inhibits cellular uptake of cobalamin (Cbl); the second type binds apo-TCII at or near the Cbl binding domain and inhibits the formation of holo-TCII; and the third binds both apo- and holo-TCII but does not interfere with Cbl binding (abstract). The antibodies were screened for epitope specificity (page 150 para. 1) and by the amount of holo-TCII immunoprecipitated on membranes as determined by radioactivity (figure 1). All three types of monoclonal antibodies will immunoprecipitate Cbl-TCII from human serum (page 151). ELISA assays were performed, where the monoclonal antibody was immobilized onto the 96 well plate; free or unbound fraction was removed; and the amount of bound content was measured (page 150 methods section).

Therefore, the claims are substantially taught by Quados et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 4 and 49 rejected under 35 U.S.C. 103(a) as being unpatentable over Quados in view of Allen et al., (US Patent 5,374,560). Quados has been discussed above however Quados et al., does not teach an assay amenable to automation. Allen et al., (US Patent 5,374,560) teaches a method of diagnosing cobalamin deficiency in humans by measuring serum levels (col. 1 lines 13-16). The method screens cobalamin deficiency using serum, urine, cerebral spinal fluid, or plasma and the assay may be provided in a kit or can be used in an automated process.

Therefore, it would have been obvious to automate the method as taught by Allen e al., because Allen et al., shows it to be conventional and well known to automate assays to detect cobalamin. Furthermore, it has been held that broadly providing a mechanical or automatic assay to replace manual activity which has accomplished the same results involves only routine skill in the art (In re Venner, 120 USPQ 192).

12. Claims 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quados et al., in view of Hoyle et al. Quados has been discussed above however Quados et al., does not teach affinity constants or degrees of cross-reactivity. Hoyle et al., (US Patent 5,451,508) teaches determination of vitamin B_{12} using monoclonal antibodies specific for B_{12} and having an affinity constant greater then $5 \times 10^{9} Mol^{-1}$. Vitamin 12 or cobalamin is present in body fluids like whole blood, plasma ans serum (col. 1 lines 16-20). Hoyle et al also teaches detaching B_{12} from its binding proteins by heat destruction or by destruction of binding proteins in the alkaline range pf pH> 13.5 (col. 1 lines 49-53). The method uses immobilized monoclonal antibodies for

clinical diagnosis (col. 2 lines 22-25). A competitive assay has proven itself to be expedient for the determination of vitamin B_{12} (col. 2 lines 35-57). The monoclonal antibodies used have an affinity constant of at least $5 \times 10^{9} Mol^{-1}$, more preferably $10^{10} Mol^{-1}$, and most preferably $5 \times 10^{10} Mol^{-1}$, as well as 100% cross reactivity with cyanocobalamin and cross reactivity with other substances of less than 0.05% through 1.5%, for vitamin B_{12} assay determination (col. 2-3 lines 64-7). The monoclonal antibodies can be used as complete antibodies, chimeric antibodies or bivalent fragments (col. 3 lines 8-10).

Therefore, it would have been obvious at the time of applicants invention to have use the antibodies of Hoyle et al., in the method of Quados et al., because the high affinity constants of the antibodies of Hoyle et al., which provide for a more sensitive assay.

13. Claims 1, 5-7, 10, 12, 16-20, 23, 26 and 40-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLean et al., in view of Houts. McLean et al., teaches several monoclonal antibodies to transcobalamin II (TCII). Three types of monoclonal antibody have been characterized: Type 1 inhibits binding of TCII to its receptor; Type 2 blocks binding of Cbl to TCII; and Type 3 can be used to immunoprecipitate TCII (page 237 para. 4). A sandwich-enzyme linked immunosorbant assay analysis of monoclonal antibody binding to TCII was performed (page 236 para. 4). The ELISA plates were coated with anti-TCII monoclonal antibodies, immobilized and found capable of binding to both or either holo-TCII and apo-TCII and show specific or preferential binding ability (table 1). The authors used biotinylated anti-

TCII monoclonal antibody and added streptavidin-peroxidase as a means of detection (page 236 para. 4). The immobilized antibodies were used to capture TCII and then detected using biotinylated monoclonal antibodies, further when the biotinylated antibody used for detection binds to an epitope overlapping with plate bound antibody used to capture TCII, a greatly reduced signal was expected (page 240 para. 1). Free cyanocobalamin was obtained from Sigma Chemical (page 235 para. 4) and tested using the monoclonal antibodies in the presence and absence of the apo-TCII receptor (page 239 para. 1). The antibodies generated can also be used to immunoprecipitate TCII in bovine serum (page 237 para. 5).However, McLean et al., does not teach a competitive binding assay or a centrifugation step to separate bound from unbound fraction.

Houts teaches a method of assaying vitamin B_{12} based on competitive binding which employs a labeled reactant which carries a group which can be readily identified (col. 1 lines 17-20). Commonly used labels are radioactive atoms and fluorescent or enzyme groups (col. 1 lines 21-22). Also, competitive binding assays use proteins which not only bind to B_{12}, but also to cobalamin analogues including transcobalamin II, R proteins and intrinsic factor (IF) present in human sera (col. 1 lines 55-66). Houts teaches a comparison of cyanocobalamin and cyanocobalamin-d-iodohistamide in a competitive protein binding assay (col. 5 lines 3-6). The tracers (cyanocobalamin and cyanocobalamin-d-iodohistamide) were diluted in a KCN mixture (col.5 line 13). A centrifugation step was performed on the supernates and the tubes were

decanted and counted (col. 5 lines 19-21). The binding proteins can be IF or a mixture of IF and R-protein (col. 5 lines 25-30). The assay also uses sample from human serum or plasma.

Therefore, it would have been obvious at the time of applicants invention to use the monoclonal antibodies to transcobalamin II both apo- and holo-TCII in a competitive sandwich ELISA assay on a solid support as taught by Houts, in the method of McLean, because Houts teaches a modified method of assaying TCII or any cobalamin analogues using samples from human plasma or serum, where a centrifuge step is performed and cyanocobalamin in either a direct or indirect assay can be assayed with any one of a variety of detectable signals can indicate presence using immobilized and non-immobilized ligands.

14. Claims 8-9, 11, 13-15, 21-22, 24 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLean et al., in view of Houts and further in view of Herbert. Neither McLean et al., nor Houts teach the dissociation of bound cobalamin, however they have been previously discussed. Herbert et al., teaches a method of selectively freeing from TCII and determining the amount vitamin B_{12} in a sample. The assay teaches detecting a decrease in the amount of vitamin B_{12} or cobalamin carried by TCII (col. 2 lines 15-19). A decrease in holo-TCII (TCII containing vitamin B_{12}) produces an increase in apo-TCII (TCII free of bound vitamin B_{12}) found in serum samples (col. 2 lines 24-32). TCII can be separated from a sample using selective antibodies (col. 3 lines 54-55) where the antibody can be coupled to a solid

support to more easily separate TCII (col. 3 lines 63-64). At pH=6, TCII binds to sephadex while the other transcobalamin proteins do not (col.3 line 65). Once the TCII-Vitamin B_{12} solution is obtained, the resulting solution may be subjected an assay for vitamin B_{12} where radioassay for vitamin B_{12} includes the removal of vitamin B_{12} from TCII for example by heating or the use of hydrochloric acid at pH=2 to destroy the TCII and removal of the B_{12} (col. 4 lines 15-20). Vitamin B_{12} dissociates from TCII when both the ionic strength and pH are low (col. 4 lines 35-37). Further assaying of vitamin B_{12} is not limited only to the detection of cobalamins, but can include the total corrinoids (col. 4 lines 54-57). The assay for vitamin B_{12} is accomplished by using a binder specific for cobalamins or for all corrinoids (col. 5 lines 10-15). In an immunoassay the binder can be a monoclonal or polyclonal antibody, a tracer is also used which can be vitamin B_{12} or an appropriate analog that is labeled with a detectable marker (col. 5 lines 16-30). The binder can be in either supported or unsupported form, and in the instances where the binder is supported, it can be supported by a solid support and the bound free fractions may be separated without the use of a separating gent, while if the binder is unsupported, then the bound free fractions can be separated by using a separating agent (col. 5 lines 33-42). Finally, in one type of assay an amount of tracer and any vitamin B_{12} present in a sample can compete for a limited number of binding sites on the binder and the amount of tracer becomes inversely proportional to the amount of vitamin B_{12} in the sample (col. 5 lines 29-34).

No more then routine skill is involved in adjusting the amount of a component of a claimed process as stated in claims 2-3, 25 and 34-36. Neither changes in concentrations nor

determining optimum concentrations which are suitable for materials have not been held to involve patentable inventions.

Therefore one skilled in the art would have expected a reasonable level of success in using an assay to include the dissociation of cobalamin/ vitamin B_{12} or analogs by changing the temperature or pH as taught by Herbert with the assay method for the determination of TCII bound cobalamin sample comprising contacting a sample body fluid with an immobilized specific binding ligand like a monoclonal antibody specific for TCII or holo-TCII, separating the bound fraction from the unbound fraction and measuring the amount of holo-TCII or TCII bound cobalamin obtained as taught by McLean et al., in view of Houts because Herbert teaches that this method is known in the art.

Prior Art

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Allen et al., (US 4,332,785) teaches immunoassay for the measurement of reticulocytes using immunoreactive material including transcobalamin II or its receptor, and method for quantitating selective immunoreactivity including fluorescent and radioactive detection employing direct or indirect labeling of the specific antibody. Kuemmerle et al., teaches an automated assay of vitamin B12. Pourfarzaneh et al., (US Patent 5,310,656) teaches a vitamin B_{12} assay where measuring of the amount of bound or unbound complex quantifies the amount of vitamin B_{12} in the sample such that the intrinsic factor:antibody complex is

measured and the value is inversely proportional to the amount of vitamin B_{12} present in the sample or the intrinsic factor:vitamin B_{12} complex is measured and the value is directly proportional to the amount of B_{12} in the sample. Pourfarzaneh et al., (US Patent 5,506,109) teaches an immunoassay kit containing site specific monoclonal antibodies, a labeled ligand, and a solid phase containing a capture ligand. Wickramasinghe et al., teaches the correlation between holo-transcobalamin II and holo-haptocorrin and total B12 in serum samples.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

January 18, 2000

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641